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An eco-safe approach to benzopyranopyrimidines and 4*H*-chromenes in ionic liquid at room temperature

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ABSTRACT

An environmentally benign, ionic liquid promoted multicomponent protocol to benzopyrano(2,3-*d*)pyrimidines and 4*H*-chromenes has been developed at room temperature. Results of the reaction depend on the nature of the nucleophile used in the reaction. Secondary amines result in the formation of benzopyrano(2,3-*d*)pyrimidines, whereas thiols give rise to 4*H*-chromenes under the same set of reaction conditions.

The challenging task of achieving 'efficiency' and 'green credentials' in all aspects of chemical synthesis, can be realized by innovative research which comprehensively addresses the issues of atom-economy, economy of steps, and the avoidance of auxiliary chemicals.[1] Multi-component reaction (MCR) protocol with environmentally benign solvents and catalytic systems is one of the most suitable strategies, which meets the requirements of green aspects of chemistry for developing libraries of medicinal scaffolds.[2] Ionic liquids are attracting increasing attention as alternative solvents for a wide range of catalytic and organic reactions due to their very low vapor pressure and non-explosive and thermally stable nature in a wide temperature range.[3] The recent years have witnessed the potential of ionic liquids as catalysts as well as reaction media aimed to develop green chemistry, avoiding the use of volatile organic solvents and allowing its reuse. There are numerous examples of all classes of organic reactions that have been successfully carried out in ionic liquid as reaction media.[4]

Benzopyrano[2,3-*d*]pyrimidine is a potentially important pharmacophore that exhibits in vivo antitumor activity, cytotoxic activity against cancer cell lines and can cause significant perturbation in cell cycle kinetics.[5] Relatively few papers have been reported on the formation of benzopyrano[2,3-*d*]pyrimidines with a limited substitution pattern. This core was initially synthesized by O'Callaghan by condensation of 2-iminocoumarin-3-carboxamides with aldehydes involving a multistep complex reaction procedure.[6] Despite some attempts to overcome the drawbacks, no benign method with promising green credentials has so far appeared for the synthesis of this core.[7] In view of the above and as a part of our ongoing research on development of efficient protocols in organic synthesis,[8] we report herein an ionic liquid promoted, efficient combinatorial synthesis of substituted benzopyrano[2,3-*d*]pyrimidines in good to excellent yields adopting a three-component one-pot tandem approach (Scheme 1). The investigations have also been extended to achieve a library of some new 4*H*-chromenes, which constitute another important class of core structures featured in a number of naturally occurring and biologically active molecules known for their antimicrobial and antifungal,[9–13] antioxidant,[14,15] antileishmanial,[16] antitumor,[17–19] hypotensive,[20] antiproliferation,[21] local anesthetic,[22] antiallergenic,[23,24] central nervous system (CNS) activities,[25] as well as for the treatment of Alzheimer's disease[26] and schizophrenia disorders.[27]

In order to optimize the reaction conditions, the catalytic activity of ionic liquids was tested for a typical multicomponent reaction of salicyldehyde **1a**, malononitrile **2**, and dimethylamine **3a** at room temperature. The results are given in Table 1.

To find out a suitable reaction medium, a number of molecular solvents were tried with catalytic amount of [Bmim]BF_4 and it was found that use of [Bmim]BF_4 with dual role of catalyst and solvent dramatically reduces the reaction time with improved product yield at room temperature (Table 1, entry 6). An elevated temperature, however, could not enhance the product yield (Table 1, entry 10). Intrigued by these observations, the model reaction was also investigated using other ionic liquids namely [Bmim]PF_6 and [Bmim]OH, but they could not afford good product yield (Table 1, entries 7 and 8).

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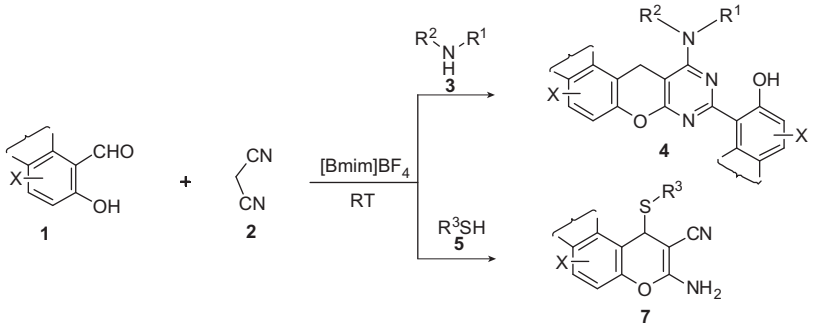
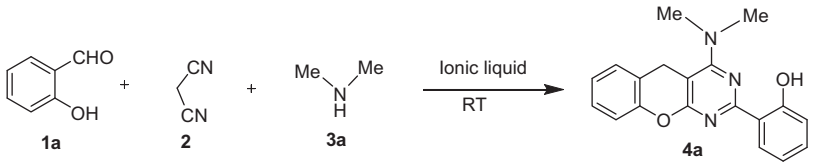


Scheme 1. Synthesis of benzopyranopyrimidines **4** and 4*H*-chromenes **5** using [Bmim]BF_4.

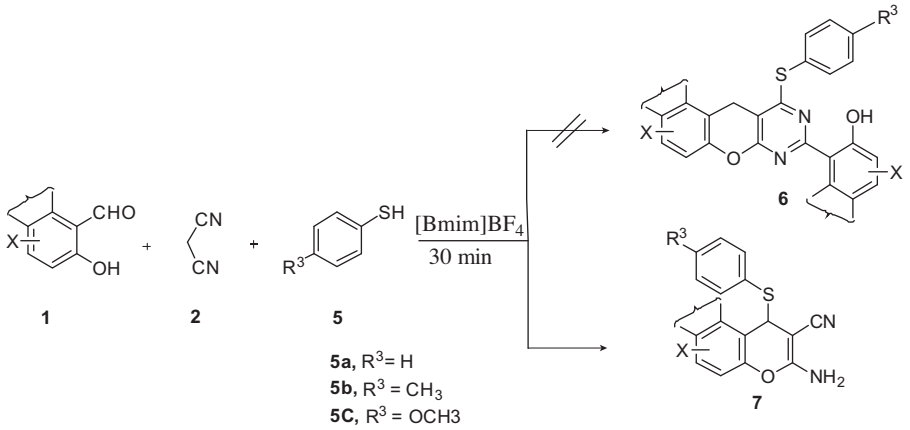
Table 1
Optimization of reaction conditions



Entry	Catalyst (mol %)	Solvent	Time	Yield[a] (%)
1	[Bmim]BF_4 (20)	1,4-dioxane	4 h	17
2	[Bmim]BF_4 (20)	EtOH	4 h	79
3	[Bmim]BF_4 (20)	Toluene	4 h	27
4	[Bmim]BF_4 (20)	Water	4 h	nr[b]
5	[Bmim]BF_4 (20)	Acetonitrile	4 h	23
6	—	**[Bmim]BF_4**	**20 min**	**88**
7	—	[Bmim]PF_6	20 min	45
8	—	[Bmim]OH	20 min	45
9	—	—	40 min	19
10	—	[Bmim]BF_4	20 min	85[c]

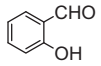
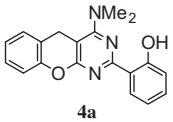
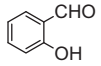
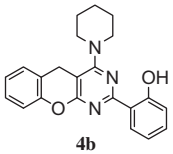
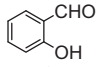
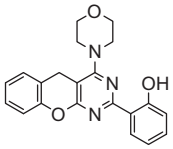
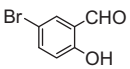
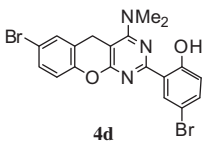
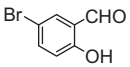
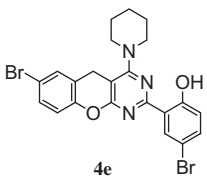
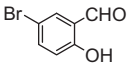
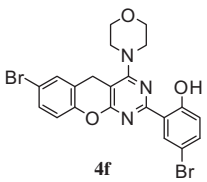
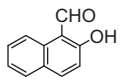
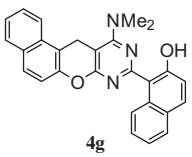
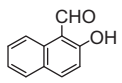
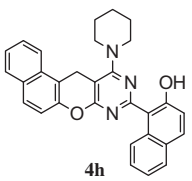
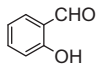
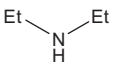
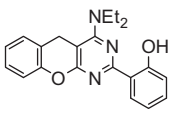
[a] Isolated yield.
[b] nr = no reaction.
[c] Reaction carried out at 60 °C.

Under the optimized set of reaction conditions, a number of salicylic aldehydes viz. salicyldehyde (**1a**), 5-bromosalicyldehyde (**1b**), and 2-hydroxynaphthaldehyde (**1c**) were allowed to react with malononitrile (**2**) and different secondary amines namely dimethylamine (**3a**), piperidine (**3b**), morpholine (**3c**), diethylamine (**3d**) to afford a variety of benzopyrano[2,3-*d*]pyrimidines **4a–i**. The outcome is described in Table 2. A perusal of Table 2 shows that salicyldehyde (**3a**) and 5-bromosalicyldehyde (**3b**) underwent the reaction smoothly affording reasonably good yields (entries 1–6). However, a considerable decrease in the product yield was observed with 2-hydroxynaphthaldehyde (**1c**) (entries 7, 8). As is evident, the secondary amines do also have profound effect on the course of overall reaction. Dimethylamine (**3a**) works well in all its reactions (entries 1, 4 and 7), but all the efforts to carry out the reaction with diethylamine (**3d**) failed (entry 9). The probable reason for this anomaly may be the presence of two extra arms,



Scheme 2. Synthesis of 4*H*-chromenes using thiols **5**.

Table 2
Synthesis[28] of substituted benzopyrano[2,3-*d*]pyrimidines (**4**)

Entry	Aldehyde	Amine	Product	Yield[a] (%)
1	 **1a**	 **3a**	 **4a**	90
2	 **1a**	 **3b**	 **4b**	84
3	 **1a**	 **3c**	 **4c**	76
4	 **1b**	 **3a**	 **4d**	78
5	 **1b**	 **3b**	 **4e**	80
6	 **1b**	 **3c**	 **4f**	75
7	 **1c**	 **3a**	 **4g**	61
8	 **1c**	 **3b**	 **4h**	65
9	 **1a**	 **3d**	 **4i**	nr[b]

[a] Isolated yield.
[b] nr = no reaction.

which must have come in the way of the reaction. However, when these arms were tied back as in the case of morpholine and piperidine, the reaction occurred comfortably (entries 2, 3, 5, 6, and 8).

Being inspired by the above results, it was thought worthwhile to replace the secondary amine with thiols under the same set of reaction conditions in order to get some newly substituted benzopyrano[2,3-*d*]pyrimidines, but to our utmost surprise, we could not achieve the formation of the expected product **6**. Careful analysis of the spectral data rather revealed the formation of 2-amino-4-arylsulfanyl-4*H*-chromene-3-corbonitriles (**7**), thereby approving a different reaction pathway (Scheme 2). The outcome of the reaction of different thiols viz. thiophenol (**5a**), *p*-methylthiophenol (**5b**), *p*-methoxythiophenol (**5c**) with salicylic aldehydes **1** and malononitrile **2** is described in Table 3. It is evident from Table 3 that all the salicylic aldehydes and thiophenols show more or less similar reactivity and product yields. The reaction was also tried with heteroaromatic and aliphatic thiols (2-mercaptobenzothiazole and 2-mercaptoethanol) but it did not succeed. The role of phenols as nucleophile in the aforementioned reaction was also tried, but it did not give any impressive results.

Table 3
Synthesis[28] of 2-amino-4-arylsulfanyl-4*H*-chromene-3-corbonitriles (**7**)

Entry	Aldehyde (**1**)	Thiol (**5**)	Product (**7**)	Yield[a] (%)
1	**1a**	**5a**	**7a**	80
2	**1a**	**5b**	**7b**	85
3	**1b**	**5a**	**7c**	82
4	**1b**	**5b**	**7d**	80
5	**1b**	**5c**	**7e**	78
6	**1c**	**5b**	**7f**	72
7	**1c**	**5c**	**7g**	81

[a] Isolated yield.

It is worthwhile to mention that the IL [Bmim]BF_4 was recycled up to five times without any significant loss and diminution in its amount and efficacy. After each and every recycle, the purity of the IL was affirmed by spectroscopic data.

In conclusion, we have demonstrated an efficient use of ionic liquid for multicomponent synthesis of benzopyrano(2,3-*d*)pyrimidines at room temperature under solvent-free conditions in an environmentally benign and one-pot fashion. The reaction has also been extended to the synthesis of 2-amino-3-arylsulfanyl-4*H*-chromene-3-corbonitriles.

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28. *General procedure for preparation of benzopyrano[2,3-d]pyrimidine* ***4***: Salicylaldehyde **1** (2 mmol), malononitrile **2** (1 mmol), secondary amine **3** (1 mmol), and $[Bmim]BF_4$ (0.2 mL) were taken in a 25 mL round bottomed flask. The reaction mixture was stirred at room temperature for 20 min. After completion of the reaction as indicated by TLC, ethanol (1 mL) and water (1 mL) were successively added while stirring. The product was filtered and washed with water and ethanol to afford pure product **4**. The aqueous phase containing the ionic liquid was washed with ether (10 mL) to remove the organic impurities, and then dried under vacuum at 90–95 °C for 2 h to afford $[Bmim]BF_4$, which was used in the subsequent runs without further purification. *2-{4-(Morpholine-4-yl)-5H-benzopyrano[2,3-d]pyrimidin-2-yl)}phenol (**4c**)* Yellow solid, mp: 196–197 °C; IR (KBr): ν 3449, 3049, 2962, 2858, 1581, 1390, 1246, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.48 (t, 4H, J = 4.2 Hz), 3.89 (m, 6H), 6.89–6.98 (m, 2H, Ar), 7.09–7.28 (m, 4H, Ar), 7.33 (t, 1H, J = 7.6 Hz, Ar), 8.38 (d, 1H, J = 7.8 Hz, Ar), 13.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 48.5, 66.5, 97.5, 116.9, 117.5, 118.2, 118.7, 118.9, 124.4, 128.1, 128.4, 129.0, 132.8, 150.2, 160.2, 161.8, 164.0, 164.5; Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.68; H, 5.24; N, 11.55. *General procedure for preparation of 2-amino-4-arylsulfanyl-4H-chromene-3-corbonitriles (**7**)*: A mixture of salicylaldehyde **1** (1 mmol), malononitrile **2** (1 mmol), thiol **5** (1 mmol) and $[Bmim]BF_4$ (0.2 mL) was stirred at room temperature for 30 min. After completion of the reaction as indicated by TLC, the product was isolated and purified adopting the same method as given in Ref. 28. *2-Amino-6-bromo-4-p-tolylsulfanyl-4H-chromene-3-carbonitrile (**7d**)* White solid, mp: 168–169 °C; IR (KBr): ν 3449, 3329, 2199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.54 (s, 2H), 4.89 (s, 1H), 6.60 (d, 1H, J = 8.7 Hz, Ar), 7.01 (m, 4H, Ar), 7.28 (m, 1H, Ar), 7.42 (m, 1H, Ar); $^{13}CNMR$ (75 MHz, DMSO-d_6): δ 20.8, 46.1, 53.1, 115.7, 117.6, 119.5, 123.8, 126.6, 129.3, 131.2, 131.3, 136.1, 138.7, 148.2, 161.8; Anal. Calcd for $C_{17}H_{13}BrN_2OS$: C, 54.70; H, 3.51; N, 7.50. Found: C, 54.60; H, 3.56; N, 7.43.